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REVIEW

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Is hepatocellular carcinoma the same disease in children and adults? Comparison of histology, molecular background, and treatment in pediatric and adult patients

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Abstract

Pediatric hepatocellular carcinoma (HCC) is rare, resulting in scattered knowledge of tumor biology and molecular background. Thus far, the variant in children has been treated as a different entity from adult HCC. We weigh the hypothesis that HCC in the pediatric and adult groups may be the same entity and may benefit from the same treatment. Although certain differences between adult and pediatric HCC are obvious and certain types of HCC may ask for a customized approach, in conventional HCC, similarities predominate, warranting treatment aiming at common molecular targets in adult and pediatric HCC patients.

KEYWORDS

adult/pediatric HCC, fibrolamellar carcinoma, hepatocellular carcinoma, liver tumor

1 | EPIDEMIOLOGY AND ETIOLOGY

Liver cancer comprises 1% to 2% of pediatric solid cancers, making the liver a rare anatomical site for pediatric cancer.[1] Hepatoblastoma and hepatocellular carcinoma (HCC) are the two most common malignant liver tumors in children.[2] In the United States, the incidence of pediatric HCC is 0.8 to 1.5 per million.[3] In the developing world, HCC is the most common malignant pediatric liver tumor, although the exact incidence in these regions is unknown.[1,2]

HCC is the most common primary liver cancer in adults and the third cause of cancer-related deaths worldwide.[4] Particularly in the Western world, the incidence is rising due to sequela of chronic hepatitis C (HCV) and alcoholic and nonalcoholic fatty liver disease.[5] The adult five-year overall survival (OS) rate remains below 12% in the United States.[5] A worldwide survival rate of more than a few months was not found in the literature. This exceedingly poor outcome may be related to frequent detection in advanced stages, no longer amenable to curative treatment. Furthermore, underlying liver disease may limit curative treatment options.

In Peru, South Africa, and many Asian countries, the introduction of hepatitis B vaccination programs has caused a decrease in the incidence of pediatric HCC.[6–8] Globally, HCC, including its rare histologically distinct variant fibrolamellar hepatocellular carcinoma (FL-HCC), occurs mostly in older children and adolescents.[9] An earlier claim that FL-HCC has a more favorable prognosis than conventional HCC could not be substantiated in a large series by Childhood Liver Tumours Strategy Group (SIOPEL).[10] Despite recent advances in treatment, OS of pediatric HCC diagnosed in advanced stages remains exceedingly poor, with five-year percentages of only 17% to 22% for all stages of pediatric HCC, including FL-HCC, in recent trials from SIOPEL and the Children's Oncology Group (COG).[11,12] Risk factors for pediatric HCC are conditions that cause hepatocellular damage such as occur in hepatitis B (HBV), HCV, autoimmune hepatitis, glycogen storage disease I–IV, Alagille syndrome, tyrosinemia, Wilson disease, hemochromatosis, alpha-1 antitrypsin deficiency, transaldolase deficiency, Gardner syndrome, familial adenomatous polyposis, Fanconi anemia, ataxia telangiectasia, primary sclerosing cholangitis, and familial progressive intrahepatic cholestasis.[2] In areas where HBV is endemic, the majority

Abbreviations: AFP, alpha-fetoprotein; AGR2, anterior gradient 2; APC, adenomatous polyposis coli protein; CASP3, caspase 3; CCNA2, cyclin A2; CCNB1, cyclin B1; CCND1, cyclin D1; CCNE, cyclin E; CDK4, cyclin-dependent kinase 4; CHIC, Children's Hepatic Tumor International Consortium; CKS2, CDC28 protein kinase 2; COG, Children's Oncology Group; CTNNB1, beta-catenin; DNA, deoxyribonucleic acid; EKB-569, pelitinib; EPCAM, epithelial cell adhesion molecule; EPHB2, ephrin type B receptor 2; FL-HCC, fibrolamellar hepatocellular carcinoma; GPOH, German Society for Pediatric Oncology and Hematology; HBV, hepatitis B; HCC, hepatocellular carcinoma; HCN-NOS, hepatocellular neoplasm not otherwise specified; HCV, hepatitis C; HGFR/c-MET receptor, hepatic growth factor receptor; HGNC, HUGO Gene Nomenclature Committee; IL13RA2, interleukin 13 receptor subunit alpha 2; JPLT, Japanese Study Group for Pediatric Liver Tumors; LAMTOR5, HBV X-interacting protein; LOH, loss of heterozygosity; MTOR, mechanistic target of rapamycin; NFKB1, nuclear factor kappa B; OS, overall survival; PDGFRB, platelet derived growth factor receptor B; PHITT, Paediatric Hepatic International Tumor Trial; RASA1, RAS p21 protein activator 1; RPS6KB1, ribosomal protein S6 kinase; SIOPEL, Childhood Liver Tumours Strategy Group; TERT, telomerase reverse transcriptase; TGFA, transforming growth factor, alpha; TGFB1, transforming growth factor beta 1; TKI, tyrosine-kinase inhibitors; TLCT, transitional liver cell tumor; VEGFA, vascular endothelial growth factor A; VEGFR/KDR, vascular endothelial growth factor receptor

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of pediatric HCC patients are chronically infected with HBV.[2] Importantly, this does not mean that these tumors develop only in cirrhotic livers, as activation of the protein LAMTOR5 (HBV X-interacting protein) or integration of HBV DNA into the hepatocyte genome can lead to chromosomal instability, suppression of tumor suppressor genes, and activation of oncogenes and set the stage for development of HCC.[5] For FL-HCC, no epidemiological risk factors are known.[10]

Pediatric cancers tend to behave differently from adult types, and some cancer types are specific to the pediatric age group. In part due to the infrequent occurrence of cirrhosis in children with HCC, pediatric HCC is thus far treated as if the variant in children is a different entity from adult HCC.[2] The biological background in which primary liver tumors arise in children and in adults appears similar: in both patient groups, the disease process is the result of a vicious cycle of damage and repair, although in most HCCs arising in adults, decades of chronic hepatic viral infection, alcohol abuse, or nonalcoholic fatty liver disease result in the end-stage, liver cirrhosis.[5]

Pediatric tumors, HCC included, appear to need fewer genetic alterations than adult cancers.[13] A possible explanation for the difference between pediatric and adult tumors is the higher basic cellular growth rate in pediatric livers.

In this review, we report our search for differences and similarities between pediatric and adult HCC to improve our understanding of pediatric HCC and to develop a scientifically based rationale for treatment.

2 | HISTOLOGY AND ETIOLOGY

The differentiation grade of HCC in pediatric patients may vary, although grade within a single tumor is mostly uniform.[14] Tumor cells resemble hepatocytes to a degree that varies according to differentiation stage; they are generally larger than their normal hepatocyte counterparts.[15] Tumor cell nuclei tend to be atypical and irregular with abundant mitoses.[14]

Cycles of damage and repair lead to disruption in related signaling pathways in HCC, as outlined below. These compounded cycles lead to hyperplasia, dysplasia, and ultimately HCC.[16]

Pediatric HCC consists of two broad categories: HCC in the context of underlying liver disease and de novo HCC.[2] De novo HCC may show three different histological types: conventional HCC, FL-HCC, or HCC with elements of hepatoblastoma.

Histology of conventional pediatric HCC is similar to histology in adults with HCC without preexisting liver disease.

FL-HCC is characterized by a histologic appearance of lamellar stroma that contains large polygonal cells with a deeply eosinophilic cytoplasm. This may contain pale bodies and hyaline globules, while the large nuclei often comprise marginalized chromatin and prominent nucleoli.[9] Certain molecular components that are aberrantly expressed in FL-HCC (discussed below) indicate that this tumor could have its origins in precursor cells of hepatocytes and biliary cells.[17]

HCC with elements of hepatoblastoma was originally termed transitional liver cell tumor (TLCT). In TLCT, HCC coexists with elements of hepatoblastoma and is most prevalent in adolescents.[18] More recently, any type of HCC/hepatoblastoma mixed tumor is by consensus named "hepatocellular neoplasm not otherwise specified" (HCN-NOS).[2,18]

3 | CYTOGENETIC AND MOLECULAR BACKGROUND

For pediatric HCC, specific associations between subtypes of histology and prognosis have not been made. Furthermore, discerning HCC from other hepatic tumors, particularly hepatoblastoma, is not always straightforward. Differentiation can be challenging, especially when alpha-fetoprotein (AFP), the main diagnostic marker in hepatoblastoma—yet also a marker of HCC—is low. AFP is secreted from HCC tumor cells; AFP level correlates with differentiation rate.[15,19] AFP was elevated in over 90% of HCC patients in a relatively large recent series of 65 patients under 20 years of age.[20] In adult HCC, AFP was elevated in approximately 70% of patients.[19] AFP correlates with tumor size,[19] thus representing an indirect marker for treatment response.

Research efforts directed at elucidating cytogenetic background and molecular biology of HCC are discussed in the following sections. All cytogenetic and molecular aberrations and correlations that will be discussed are significant findings from the respective cited studies. HUGO Gene Nomenclature Committee (HGNC)–approved abbreviations are used throughout.

3.1 | Cytogenetic background

Most cases of adult human HCC are aneuploid, suggesting integration of tumor deoxyribonucleic acid (DNA) and chromosomal instability. Recurrent gains are reported at 1q, 8q, and 20q.[21,22] Common losses in adult HCC are found at 4q, 8p, 13q, 16q, and 17p.[21–23] Loss of 8p was found to be specific for HCC; it did not occur in evaluated FL-HCC (or hepatoblastoma) cases.[23] This locus may, therefore, contain genes that cause FL-HCC and/or suppress HCC. The amplified regions of 1q, 6p, and 17q contain genes with roles in angiogenesis, such as *VEGFA* (vascular endothelial growth factor A), and in development and differentiation, such as *RPS6KB1* (ribosomal protein S6 kinase), while the region of loss at 4q contains apoptosis-related *CASP3* (caspase 3).[24] This latter loss inhibits apoptosis and, therefore, furthers unlimited growth. Strikingly, when comparing imbalances in adult HCC with those in hepatoblastoma, gains in chromosomes 1, 8, and 20 are common in both tumor types.[25–27]

Few studies were done on the cytogenetic background of HCC in the pediatric population specifically. A comparison of nine childhood and nine adult HBV-positive cases found more frequent loss of heterozygosity (LOH) of 13q in pediatric HCC and LOH of 8p and 17p, with similar frequencies in pediatric and adult cases.[28] Interestingly, 13q contains the locus of the tumor suppressor gene *RB1*, which is involved in cell-cycle control when functional, and is associated with late progression and more aggressive HCC when disabled.[29] Deletion of the distal part of chromosome 11p was found in HCN-NOS.[13]

The combination of gain of chromosome 4q and losses at 9p, 16p, and Xq is specifically found in FL-HCC.[23] Although series in

TABLE 1 Cytogenetic aberrations in adult and pediatric HCC

Locus	Adult HCC	Pediatric HCC	HCN-NOS	FL-HCC
1q	Gain			
4q	Loss			Gain
8p	Loss/LOH	LOH		Normal
8q	Gain			
9p				Loss
11p			Partial loss	
13q	Loss	LOH		
16p				Loss
16q	Loss			
17p	Loss/LOH	LOH		
20q	Gain			
Xq				Loss

Abbreviations: FL-HCC; fibrolamellar hepatocellular carcinoma; HCC; hepatocellular carcinoma; HCN-NOS; hepatocellular neoplasm not otherwise specified; LOH; loss of heterozygosity.

pediatric HCC and FL-HCC are scarce and small in size, chromosomal aberrations may provide clues for causative and suppressing genes.

Taken together, these chromosomal imbalances suggest that aberrations in the growth, development, differentiation, apoptosis, angiogenesis, and cell-cycle control pathways are at the base of HCC. This fits well with the observed mechanism of hepatocarcinogenesis; although there are different types of HCC, generally these tumors are the result of compounded cycles of damage and repair. Aberrations in the processes involved in repair ultimately lead to cancer. Cytogenetic aberrations are summarized in Table 1.

3.2 | Molecular background

The WNT/CTNNB1 (beta-catenin), EPHB2 (ephrin type B receptor 2), and TGFB1 (transforming growth factor beta 1)/MTOR (mechanistic target of rapamycin) signaling routes involved in growth, development, and differentiation are commonly aberrantly activated or repressed in conventional type pediatric as well as adult HCC.[13,16] Furthermore, angiogenesis and apoptosis pathways are often deregulated.[16] Significantly, aberrant pathways are briefly discussed below. Where available, findings from pediatric cases are discussed.

3.2.1 | Growth, development, and differentiation: The WNT/CTNNB1, EPHB2, and TGFB1/MTOR signaling routes

WNT/CTNNB1 pathway

The WNT/CTNNB1 pathway is involved in enhancing proliferation and differentiation of cells. Mutation of *CTNNB1* is a major causative genetic alteration in adult HCC, accounting together with mutation of *TP53* (tumor protein p53; see below) for the two most prevalent genetic alterations.[16,21] Activation of WNT signaling is a principal component of hepatocarcinogenesis.[13] Interestingly, *CTNNB1* mutation in adult HCC correlates with absence of underlying liver disease and a high differentiation grade, which may translate clinically in patients presenting with larger tumors.[30] The absence of underlying liver disease in these adult tumors may point to parallels with certain cases of childhood HCC. In pediatric HCC, nuclear CTNNB1 expression was reported in a well-differentiated tumor; CTNNB1 was found along with E-cadherin expression, and somatic driver mutations in *CTNNB1* were reported.[31–33] *CTNNB1* and *TERT* (telomerase reverse transcriptase) promoter mutations occurred in three cases of HCN-NOS.[13] The *TERT* mutations were exclusive to HCN-NOS and occurred together with high levels of AFP, suggesting that HCN-NOS in these cases arises from HB rather than early-onset HCC. Overall, aberrations in CTNNB1 and other components of this pathway appear to be connected to tumor differentiation and form an early and crucial event in hepatocarcinogenesis.

EPHB2 pathway

The EPHB2 pathway is involved in cellular motility, division, and differentiation. EPHB2 expression is associated with disease progression of HCC in adults.[34] RAF1 is found in late stages of HCC. In contrast, RASA1 (RAS p21 protein activator 1) involvement in HCC was found in more differentiated HCC and in early FL-HCC.[34] Upregulation of the c-MET receptor (a.k.a. hepatic growth factor receptor, HGFR) is associated with vascular invasion and poor prognosis in adult HCC.[35] Interestingly, in contrast, a comparison of 10 childhood HCCs with 16 adult HCC cases, 21 cholangiocarcinomas, and 28 hepatoblastomas showed that the *MET* gene was exclusively mutated in pediatric HCC.[36] Taken together, EPHB2 pathway disruptions are reported in both adult and pediatric HCC and are predominantly connected to tumor progression, likely representing a later phenomenon in hepatocarcinogenesis.

TGFB1/MTOR pathway

The TGFB1/MTOR signaling pathway regulates cellular proliferation, differentiation, and growth. Loss of the tumor suppressor *PTEN* correlates with increased levels of phosphorylated AKT1 and MTOR in adult HCC.[37] These aberrations are associated with advanced tumor grade, increased intrahepatic metastasis, vascular invasion, a higher TNM stage, and a high MKI67 (a.k.a. Ki-67) index.[37] Taken together, these changes lead to uncontrolled protein synthesis resulting in tumor growth. No reports from pediatric HCC series were found, indicating an unexplored field that should be investigated.

3.2.2 | Angiogenesis, apoptosis, and cell-cycle control signaling routes

Angiogenesis pathway

Expression of EGFR, the receptor of TGFA (transforming growth factor, alpha), was found in 68 of 100 samples of adult HCC examined and correlated with proliferation, stage, intrahepatic spread, and tumor differentiation.[38] Increased KDR (a.k.a. vascular endothelial growth factor receptor, VEGFR) expression correlates with male gender, higher tumor differentiation grade, HbsAg positivity, and cirrhosis.[35] Increased PDGFRB (platelet-derived growth factor receptor B) expression is associated with plasma AFP concentration, tumor size, cirrhosis, and OS.[35] In conclusion, increases in expression of angiogenesis pathway factors are ubiquitous in adult HCC and correlate with parameters in all stages of the disease. Strikingly, no pediatric HCC reports were found, even though the angiogenesis inhibitors sorafenib and aflibercept are empirically used to treat pediatric HCC.

Both drugs have shown success in small series thus far.[39,40] Clearly, this is an unexplored area of research worthy of attention.

Apoptosis pathway

As previously discussed, mutation of *TP53* is highly frequent in adult HCC. Interestingly, *TP53* and *CTNNB1* mutations are not common in FL-HCC.[16,30] Hepatocarcinogenesis induced by Aflatoxin-B1 contaminated food and HBV is specifically linked to an arginine to serine substitution at codon 249 of exon 7 of *TP53*.[41] Loss of *TP53* and *CDKN2A* correlates with advanced stage.[42] Deletion of *TP53* was found in HCN-NOS.[31] The apoptosis regulator GATA4 was expressed in childhood HCC, but not in adult HCC.[43] As it is also absent from late fetal and postnatal liver, it may represent a marker in certain cases of pediatric HCC. Induction of GATA4 is seen especially in patients with hereditary tyrosinemia type 1.[43] Overall, changes in apoptosis pathway components are linked to adult HCC of variable etiology as well as to pediatric HCC, although different components are aberrant in these tumor types. Given their frequency, alterations in this pathway are likely essential for hepatocarcinogenesis.

Cell-cycle control pathways

Expression of the cell proliferation marker PCNA and the cell-cycle regulators CDK4 (cyclin-dependent kinase 4), CCNB1 (cyclin B1), CCNA2 (cyclin A2), and CKS2 (CDC28 protein kinase 2) was found in a low survival subclass of adult HCC in a gene-expression-profiling effort in 89 HCCs.[44] Deletions of the cell-cycle checkpoint guardian RAD17 were found in HCN-NOS.[13] The previously discussed study that compared childhood and adult HBV-positive cases found lower levels of the downstream CTNNB1 target CCND1 (cyclin D1) in childhood HCC and similar levels of CDK4 and CCNE1 (Cyclin E)—which is believed to substitute for CCND1 function in its absence.[28] CCND1 was present in advanced-stage pediatric HCC in another study.[32] As several components of these pathways are downstream targets of the major player CTNNB1, unsurprisingly, many of these factors are themselves dysregulated in hepatic cancer. Similar to the situation for the apoptosis pathway, different components are altered according to the type of cancer, possibly defining the type.

3.2.3 | Other pathways aberrant in hepatocarcinogenesis

Transcriptional, translational, and posttranslational modification pathways

The importance of deregulation of transcription-regulatory components was exemplified by mutations in the corepressor *GON4L*, the coactivators *PRIC285* and *SGF29*, and the transcription factors *MYC*, *GATA6*, *HOXD11*, *PRDM10*, and *NFX1* in HCN-NOS.[13] With respect to mutations with a posttranslational effect, the ubiquitin E3 ligase gene *HUWE1* was affected. Mutation of *CTNNB1* also has a posttranslational effect, as it results in dysfunctional phosphorylation sites, preventing the proteasomal degradation of CTNNB1 via a complex containing APC (adenomatous polyposis coli protein).[13] Upregulation of genes involved in ubiquitination and ubiquitination-like pathways was found in an ominous prognosis subclass of HCC, suggesting etiologic involvement of these signaling routes in disease progression.[44] High levels of the phosphorylated form of transcription factor NFKB1 (nuclear factor kappa B, subject to ubiquitination) specifically in FL-HCC may serve as a diagnostic marker as it is absent from nonneoplastic liver tissue.[45]

3.2.4 | Cellular migration, transformation, and stress response pathways

Recently, the fusion product of *DNAJB1* and *PRKACA* was detected as a specific and sensitive marker for FL-HCC, not occurring in HCC.[46] *DNAJB1* codes for a heat shock protein active in cellular stress responses and *RPKACA* encodes the catalytic domain of protein kinase A, which regulates a myriad of cellular processes through phosphorylation.

Furthermore, the hepatobiliary precursor cell markers KRT7, ETFA, CEACAM5, IL13RA2 (interleukin 13 receptor subunit alpha 2), and EPCAM (epithelial cell adhesion molecule), and the cellular migration and transformation component AGR2 (anterior gradient 2), are aberrantly expressed in FL-HCC and may assist in distinguishing between FL-HCC and HCC.[17,47]

Taken together, despite the limited number and size of molecular biological studies in pediatric HCC, this overview shows that growth, development, and differentiation signaling pathways are commonly aberrant in both pediatric and adult HCC, often in comparable ways. These pathways are crucial in cell repair, in line with the observed cycles of damage and repair at the base of HCC. Furthermore, components of the angiogenesis, apoptosis, and cell-cycle control pathways are often dysregulated—albeit differently in the distinct tumor types. Differences in biological behavior may be defined by the molecular components that are aberrant in these pathways and whether they are upregulated, downregulated, or absent. Molecular components in these pathways are logical targets. Molecular aberrations in pediatric and adult HCC are summarized in Table 2. Current therapies are discussed next.

4 | CURRENT NONSYSTEMIC TREATMENT MODALITIES

Irrespective of the underlying molecular changes, HCC diagnosed in earlier stages may be cured with complete tumor resection with or without orthotopic liver transplantation, radio-frequency ablation, and (chemo-) embolization.[1,2] Especially in pediatric HCC, the liberal use of liver transplantation omitting the Milan criteria described for adult patients is increasingly advocated.[48] The Milan criteria comprise as requirements that the cancerous process does not consist of more than one solitary nodule with a maximum diameter of five centimeters, or three nodules measuring each maximally three centimeters, and that no vascular invasion or extrahepatic manifestation is present.[49] For FL-HCC, the only effective treatment is complete resection.[10]

5 | TARGETED THERAPIES IN CLINICAL TRIALS

The aforementioned treatment modalities rarely yield lasting results in advanced or recurring HCC. Although many agents have been developed and tested, efficacious chemotherapeutic options are limited.

TABLE 2 Molecular aberrations in adult and pediatric HCC

Pathway	Molecular component	Adult HCC	Pediatric HCC	HCN-NOS	FL-HCC
WNT/CTNNB1					
	CTNNB1	Δ	Δ	Δ	None
	CTNNB1	+/++	+/++		
	E-cadherin		+		
	TERT			Δ	
EPHB2		+			
	RAF1	+			
	RASA1	+			+
	HGFR	++			
	MET		Δ		
TGFB1/MTOR					
	PTEN	-			
	AKT1	++			
	MTOR	++			
Angiogenesis					
	EGFR	+			
	TGFA				
	VEGFR	++			
	PDGFRB	++			
Apoptosis					
	TP53	Δ/−		−	None
	CDKN2A	−			
	GATA4	-	+		
Cell-cycle control					
	PCNA	+			
	CDK4	+	+		
	CCNB1	+			
	CCNA2	+			
	CKS2	+			
	RAD17			−	
	CCND1		−/+		
	CCNE1	+	+		
Transcriptional/translational/ posttranslational modification					
	GON4L			Δ	
	PRIC285			Δ	
	SGF29			Δ	
	MYC			Δ	
	GATA6			Δ	
	HOXD11			Δ	
	PRDM10			Δ	
	NFX1			Δ	
	HUWE1			Δ	
	NFKB1				++
Cell migration/transformation/ stress response					
	DNAJB1/RPKACA	-			+

(Continues)

TABLE 2 (Continued)

Pathway	Molecular component	Adult HCC	Pediatric HCC	HCN-NOS	FL-HCC
	KRT7				++
	ETFA				++
	CEACAM5				++
	IL13RA2				++
	EPCAM				++
	AGR2				++

Δ, Mutation; ++, upregulation; +, expression/presence; -, absence; –, downregulation; —, loss.
Abbreviations: AGR2, anterior gradient 2; CCNA2, Cyclin A2; CCNB1, Cyclin B1; CCND1, Cyclin D1; CCNE1, Cyclin E; CDK4, cyclin dependent kinase 4; CKS2, CDC28 protein kinase 2; CTNNB1, beta-catenin; EGFR, endothelial growth factor receptor; EPCAM, epithelial cell adhesion molecule; EPHB2, ephrin type B receptor 2; FL-HCC, fibrolamellar hepatocellular carcinoma; HCC, hepatocellular carcinoma; HCN-NOS, hepatocellular neoplasm not otherwise specified; HGFR, hepatic growth factor receptor; IL13RA2, interleukin 13 receptor subunit alpha 2; MET, mesenchymal to epithelial transition; MTOR, mechanistic target of rapamycin; NFKB1, Nuclear Factor kappa B; PDGFRB, platelet derived growth factor receptor B; RASA1, RAS p21 protein activator 1; TERT, telomerase reverse transcriptase; TGFA, transforming growth factor, alpha; VEGFR, vascular endothelial growth factor receptor.

TABLE 3 Current targeted therapies in adult HCC

Prime target → agent ↓	VEGFA	PDGFRB	RAF1/MAP2K2/ EPHB2	EGFR	PIK3CA/ AKT1/MTOR	MET/ HGF	HSP90AA1	FGF1/ HPSE	TNFRSF 10A
Sorafenib	X	X	X						
Regorafenib	X	X	X						
Aflibercept	X	X							
Sunitinib	X	X							
Brivanib	X	X							
Bevacizumab	X	X							
Ramucirumab	X	X							
TSU-68	X	X							
Linifanib	X	X							
Cediranib	X	X							
Pazopanib	X	X							
Lenvanib	X	X							
Lenalidomide	X	X							
Axitinib	X	X							
Erlotinib				X					
Gefitinib				X					
Lapatinib				X					
Cetuximab				X					
Everolimus					X				
Temsirolimus					X				
Sirolimus					X				
Rapamycin					X				
Selumetinib			X						
Refametinib			X						
Tivantinib						X			
Cabozantinib						X			
Ganetespib							X		
PI-88								X	
Mapatumumab									X

Abbreviations: EGFR, endothelial growth factor receptor; EPHB2, ephrin type B receptor 2; FGF1, fibroblast growth factor 1; HCC, hepatocellular carcinoma; HGF, hepatic growth factor; HPSE, heparanase; HSP90AA1, heat shock protein 90 alpha family class A member 1; MAP2K2, mitogen-activated protein kinase 2; MET, mesenchymal-to-epithelial transition; MTOR, mechanistic target of rapamycin; PDGFRB, platelet-derived growth factor receptor B; PIK3CA, phosphatidylinositol-4,5-bisphophate 3-kinase catalytic subunit alpha; TNFRSF10A, tumor necrosis factor receptor superfamily member 10A; VEGFA, vascular endothelial growth factor receptor.

TABLE 4 Current targeted therapies in pediatric HCC

Prime target → agent ↓	VEGFA	PDGFRB	RAF1/MAP2K2/EPHB2	CTNNB1	CCND1	NFKB1
Sorafenib	X	X	X			
Aflibercept	X	X				
Curcumin				X	X	X

Abbreviations: CCND1, Cyclin D1; CTNNB1, beta-catenin; EPHB2, ephrin type B receptor 2; HCC, hepatocellular carcinoma; MAP2K2, mitogen-activated protein kinase 2; NFKB1, nuclear factor kappa B; PDGFRB, platelet-derived growth factor receptor B; VEGFA, vascular endothelial growth factor receptor.

From the wide array of molecular players implicated in hepatocarcinogenesis, a number of attractive targets in human HCC have been established. Agents targeting these actors include tyrosine-kinase inhibitors (TKI) with names ending in "nib" and monoclonal antibodies with names ending in "mab." Currently used agents and their targets in adult HCC are displayed in Table 3.[24,30,40,50,51]

A recent meta-analysis of targeted agents used in advanced adult HCC shows that sorafenib combined with erlotinib may be the most effective regimen.[42,51,52] Current chemotherapeutic treatment of adult patients with advanced HCC (and an otherwise decent performance status) consists of sorafenib or a sorafenib-based regimen.[42,51,52] In a small retrospective study, the German Society for Pediatric Oncology and Hematology (GPOH) added sorafenib on a "compassionate use" base to cisplatin and doxorubicin in pediatric HCC, with promising results (6 of 12 patients were in complete remission after a median follow-up of 20 months).[39] A prospective phase III trial evaluating the efficacy of sorafenib in relapsed or refractory pediatric HCC is currently run by COG. However, acquired resistance to sorafenib is an important issue. The second-generation TKI EKB-569 (pelitinib), which, in addition to EGFR and KDR, also targets ERBB2 (a.k.a. HER2NEU), shows promise in multi-drug-resistant cells *in vitro*.[53] A synergistic effect was observed in highly resistant cells when a combination of EKB-569 and sorafenib was applied.

Stable disease in a pediatric HCC patient was seen in a phase I trial of the VEGF-trapping agent aflibercept.[40] Worth mentioning is the preliminary promise of curcumin in pediatric HCC cell lines and orthotopic models.[54] This phytochemical with few side effects in adult patients has shown antitumor effects in adult HCC. NFKB1, CTNNB1, and CCND1 are its molecular targets. All of these targets have significant roles in pediatric HCC as described above. Targeted therapies with potential efficacy in pediatric HCC are shown in Table 4.

Combining drugs to enhance the effects of sorafenib, while targeting multiple molecular pathways at once, may at present be the approach of choice in advanced HCC. However, currently available treatments lead to stable disease (tumor necrosis, no decrease in size) at best and should thus be regarded as palliative treatment with only modest gain in survival and quality of life.[42,51]

6 | CONCLUSION AND WAY FORWARD

Rather than a divide in pediatric and adult HCC, there appears to be a distinction in HCC types based on origination in healthy liver or liver compromised by inflammatory or metabolic disease. Taking the commonly aberrant WNT/CTNNB1 pathway as an example, mutation or increased expression of CTNNB1 is reported in well-differentiated HCC without underlying inflammatory liver disease in both adult and pediatric patients. Types of HCC may thus be characterized by the way in which signaling pathway components are altered.

Given the epidemiology, most data are generated from adult HCC patients. Pronounced aberrations of the angiogenesis pathway were found in certain adult HCC cases and may be related to cirrhosis.[32] No data on angiogenesis signaling in pediatric HCC are available. Even without these data, we argue that for a strategy treatment to be effective, the type of HCC and its molecular changes rather than the age group matters. Thus, the most successful treatment strategies based on recurrent molecular abnormalities obtained from adult patients may be effective in certain pediatric patients. The efficacy of the angiogenesis inhibitor sorafenib in adults and its early promise in pediatric patients exemplifies this approach.[36]

Furthermore, international collaboration initiatives, such as Children's Hepatic Tumor International Consortium (CHIC) and the upcoming Paediatric Hepatic International Tumor Trial (PHITT), are essential for progress in pediatric HCC given the low incidence of these tumors.[2,10] These initiatives may allow for a research effort to define the molecular aberration profiles at the origin of the different HCC tumor types to facilitate the search for effective targeted agents.

In conclusion, the molecular background of the diverse HCC types needs to be further elucidated. Apart from specific types of HCC, which predominantly occur in older pediatric and adolescent patients (HCC in patients with underlying liver diseases or with familial cancer syndromes; FL-HCC or HCN-NOS), too few arguments currently remain for a distinction in treatment of HCC based on age group.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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